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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,099	06/11/2007	Ha-Soon Choi	PAT033685-US-PCT	6685

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NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
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EXAMINER	
MOORE, SUSANNA	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
08/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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PATRICIA.HOFSTETTER@NOVARTIS.COM

Office Action Summary	Application No.	Applicant(s)	
	10/589,099	CHOI ET AL.	
	Examiner	Art Unit	
	SUSANNA MOORE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *8-10 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/27/10,7/23/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 5/14/2010 is acknowledged. Group I, drawn to pyrrolo[2,3-d]pyrimdines and compositions thereof, embraced by claims 1-7 was elected by Applicant. The traversal is on the ground(s) that "Applicants have amended claim l to delete "heterocycloalkylalkyl" from R_2. The amended claims do not cover the multi-substituted tetrahydrofuranyl core defined as Formula I in US 20050272676 A1." This is not found persuasive because according to MPEP §803 "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Applicant has amended the claims but after the restriction requirement. The requirement is still deemed proper and is therefore made **FINAL**.

There are 11 claims pending and 9 under consideration. Claims 1-6 and 11 are compound claims. Claim 7 is a composition claim. Claims 8 and 9 are method of using claims, which are withdrawn from consideration. Claims 11 and 12 are new claims. This is the first action on the merits. The application concerns some pyrrolo[2,3-d]pyrimidine compounds, compositions, synthesis, and uses thereof.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Substituted Pyrrolo[2,3-d]pyrimidines as Protein Kinase Inhibitors.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 7/23/2008 and 7/27/10 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

This application contains claims 8, 9 and 12, drawn to an invention nonelected with traverse in the paper of 5/14/2010. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claim 11 is objected to because of the following informalities: some of the structures have overlapping atoms, see page 19, the left hand side, second compound. This is just one example. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "radicals" in found throughout claims 1-3 is vague. The term "radical" is a chemical term which could define a free radical, an atom or molecule that bears an unpaired electron. Applicant should change the term to "group" if this is what Applicant intends.

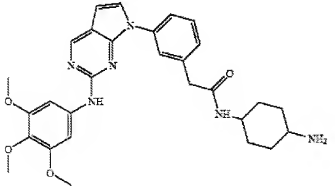
The term "formamyl" in claims 3 and 4 is vague. Applicant has not defined this substituent in the Specification.

The term "ethyl-(2-hydroxy-ethyl)-amino 2-(4-methyl-piperazin-1-yl)-ethoxy" in claim 3 is lacks antecedent basis. Applicant has not defined this substituent in the Specification.

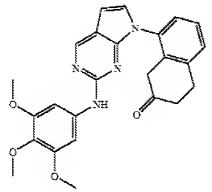
The term "heteroarylakyl" in claim 3, line 3 lacks antecedent basis.

The term "carboxy" in claim 4 is vague. This is the name of functional group and not a substituent. Applicant has not defined this substituent in the Specification.

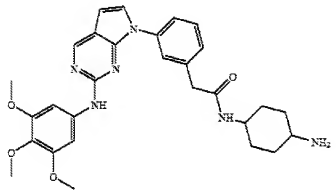
In claim 11, the following compounds lack antecedent basis:



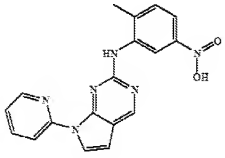
, see page 11, right hand column, second compound;



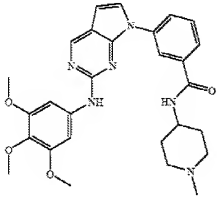
, see page 15, right hand column, second compound;



, see page 18, right hand column, first compound;

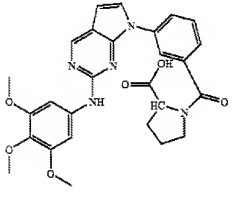


, see page 18, left hand column, third compound;



, see page 26, left hand column, last compound;

and



, see page 27, left hand column, third compound.

The term "formamidyl" in claim 4 lacks antecedent basis. Said tem is a N=C-N, and this term is not found in claim 1 as a substituent on R_2. Said term is found throughout claim 4.

The alkoxy groups on formula Ig in claim 6 lacks antecedent basis due to the alkoxy groups on the phenyl ring of R_1.

Claims 1-7 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Specification does not provide specific description for "isomers," and just a mere recitation of "isomers" is not sufficient to comply with the written description requirement. There are many different kinds of isomers, e.g. regioisomers, constitutional isomers, stereoisomers, etc. Constitutional isomers are isomers with different connectivity that have the same molecular formula. For example, n-propanol and methyl ethyl ether have the same molecular formula, C_3H_8O. What are these "isomers?" What do they look like? Where does Applicant teach how to make these "ismoers?" Did Applicant have possession of these "isomers?" Do these isomers still meet the requirements of formula (I) in claim 1?

Claims 1-7 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts of the compounds of claim 1, does not reasonably provide enablement for a polymorph or solvate of a compound of claim 1. The specification does not provide sufficient guidance nor does it enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention is a compound of claim 1, or a pharmaceutically acceptable salts of said compounds. There is not a general teaching of solvates of the compounds of claim 1 in the specification.

The state of the prior art and predictability or lack thereof in the art

It is the state of the prior art that the term "solvate" found in the claims is defined as a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute. It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. Predicting the formation of polymorphs or solvates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely

to the possible formation of solvates and hence generalizations cannot be made for a series of related compound (See Vippagunta, et al.)

The scope of "solvate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active in vivo. Solvates can not be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance present in the specification or working examples present in the specification are that defines or relates to what hydrates or solvates are being included in the elected invention.

The breadth of the claims

The breadth of the claims is a compound of claim 1 or a pharmaceutically acceptable salt or hydrates or solvate thereof.

The quantity of experimentation needed and the level of the skill in the art

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with various solvents without any direction as to what compounds form hydrates or solvates with which solvents.

The level of skill in the art is high without showing or guidance as to how to make solvates or polymorphs of a compound of claim 1 it would require undue experimentation to

figure out the solvents, temperatures and reaction times that would provide hydrates or solvates of the above compounds.

To overcome this rejection, Applicant should submit an amendment deleting the terms "hydrates, solvates" or provide evidentiary support for polymorphs or solvates.

Claims 1-7 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The [eight] factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be

biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in paragraphs 0084 and 0085, page 17. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of

the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list potential prodrug derivatives embraced by claim 1.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug. The Examiner suggests deleting the phrase "prodrugs" from said claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Chkhikvadze et. al. (SU 194829).

The reference teaches the following compounds:

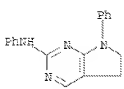
L4 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1968:427444 CAPLUS
DOCUMENT NUMBER: 69:27444
ORIGINAL REFERENCE NO.: 69:5123a,5126a
TITLE: Preparation of 7-substituted 5,6-dihydropyrrolo[2,3-d]pyrimidines or its derivatives
INVENTOR(S): Chkhikvadze, K. A.; Koretskaya, N. I.; Magidson, O. Yu.; Rodnyanskaya, N. S.
PATENT ASSIGNEE(S): Ordzhonikidze, S., All-Union Scientific-Research Chemical-Pharmaceutical Institute
SOURCE: U.S.S.R. From: Izobret., Prom. Obraztsy, Tovarnye Znaki 1967, 44(9), 45.
CODEN: URXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Russian
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
SU 194829		19670412	SU	19660708

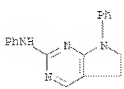
AB To obtain 7-alkyl(aryl) derivs. of the title compds., 6-(alkyl)arylamino-5-(β-haloethyl)pyrimidines or derivs. there of are treated at 140-50° in a high boiling solvent, e.g. ethylene glycol.

IT 19144-66-2P 19144-67-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 19144-66-2 CAPLUS
CN 5H-Pyrrolo[2,3-d]pyrimidin-2-amine, 6,7-dihydro-N,7-diphenyl- (CA INDEX NAME)



RN 19144-67-3 CAPLUS
CN 5H-Pyrrolo[2,3-d]pyrimidin-2-amine, 6,7-dihydro-N,7-diphenyl-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

, which is embraced by claim 1. Thus, said claims are anticipated by Chkhikvadze et. al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

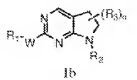
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Yang et. al. (US 20040224964). The reference is a 102(e) date.

The instant Application claims compounds of formula Ib, wherein R_1= 2,4,6-trimethylphenyl, W= NH, R_2= cycloalkyl, R_3= hydrogen and n= 0.



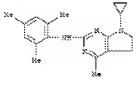
Ib

The reference teaches the following compounds:

RN 790696-41-5 CAPLUS
CN 5H-Pyrrolo[2,3-d]pyrimidin-2-amine,
7-cyclopropyl-6,7-dihydro-4-methyl-N-[2,4,6-trimethylphenyl]-,
2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 790696-47-4
CMF C19 H24 N4



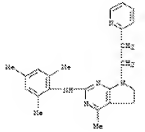
CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 791696-70-8 CAPLUS
CN 5H-Pyrrolo[2,3-d]pyrimidin-2-amine,
6,7-dihydro-4-methyl-7-[2-[2-(2-pyridinyl)ethyl]-5-(2,4,6-trimethylphenyl)-,
2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 791696-69-5
CMF C22 H27 N5



CM 2

CRN 76-05-1
CMF C2 H F3 O2

, see columns 15-16

for these specific compounds, 3 and 4, respectively. The compositions are found in column 77, line 20. is a methyl versus Applicant's hydrogen substituent at the 4-position of the pyrrolo[

The only difference between the compounds in the instance application and reference 2,3-d]pyrimidine bicycle. Since a methyl group is considered a homolog of hydrogen these compounds are considered equivalent. The MPEP 2144.09 states "Compounds which are… homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). Also, note *In re Magerlein*, 202 USPQ 473; *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr,* 137 USPQ 548.

Thus, claims 1-5 and 7 are rendered obvious by O'Yang et. al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSANNA MOORE whose telephone number is (571)272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susanna Moore/
Examiner, Art Unit 1624